Title: A Single-Arm, Multicenter, Phase 2 Study of Brigatinib in Japanese Patients With ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

NCT Number: NCT03410108

Statistical analysis plan Approve Date: 13-Jul-2020

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Brigatinib-2001

A Single-Arm, Multicenter, Phase 2 Study of Brigatinib in Japanese Patients With ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

PHASE 2

Version**:** Amendment 6

Date**:** 13 Jul 2021

Prepared by:

PPD

Based on:

Protocol Version: Amendment 4

Protocol Date: 22 Jul 2020

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BUN	blood urea nitrogen
CL/F	oral clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CxDx	Cycle x Day x
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DLSS	Dohmen Life Science Services
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOPE	early onset pulmonary event
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	the 5-level version of the EuroQol 5-dimensional questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice

G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage-colony stimulating factor
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
iDOR	duration of intracranial response
IGF1R	insulin-like growth factor receptor 1
ILD	interstitial lung disease
iORR	intracranial objective response rate
iPFS	intracranial progression-free survival
IRB	institutional review board
IRC	independent review committee
IUD	intrauterine device
KD	kinase domain
KL-6	Krebs von den Lungen-6
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PP	per-protocol
PR	partial response

PRO	patient-reported outcome
QD	once daily
QLQ	Quality of Life Questionnaire
QOL	quality of life
QTc	heart rate-corrected QT interval (calculated)
QTcF	corrected QT interval by the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros oncogene 1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameters
SMQ	symptoms standardized Medical Dictionary for Regulatory Activities query
SP-D	surfactant protein-D
SpO_2	percutaneous oxygen saturation
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of the normal range
US	United States
WBRT	whole brain radiation therapy
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to evaluate efficacy of brigatinib in Japanese patients with ALK-positive advanced NSCLC.

- ORR will be evaluated in the refractory patients.
- PFS rate at 12 months in Kaplan-Meier plots (12 months PFS rate) will be evaluated in the TKI-naïve patients.

4.2 Secondary Objectives

The secondary objectives are:

- To confirm the clinical dose in Japanese patients.
- To characterize the efficacy of brigatinib as shown by following parameters
  For all enrolled patients (including TKI-naïve patients): DOR, PFS, disease control rate (DCR), time to response, and overall survival (OS).
  For the TKI-naïve patients: ORR
- To characterize the intracranial efficacy of brigatinib, as evidenced by iORR, duration of intracranial response (iDOR), and iPFS in patients with intracranial disease at baseline, from refractory and TKI-naïve cohorts.
- To assess patient-reported outcomes (PROs) of health-related quality of life (HRQOL) and symptoms of lung cancer with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3.0), its lung cancer module QLQ-LC13, and the 5-level version of the EuroQol 5-dimensional questionnaire (EQ-5D-5L).
- To characterize the PK of brigatinib in Japanese patients.

4.3 Safety Objectives

The safety objective is to assess the safety and tolerability of brigatinib.

4.4 CCI [redacted]

CCI [redacted]

4.5 Study Design

This is a nonrandomized, multicenter, phase 2, open-label study with a safety evaluation lead-in, to evaluate the efficacy and safety of brigatinib in Japanese patients with ALK-positive advanced NSCLC.

The study consists of the safety evaluation lead-in part and the expansion part. The safety evaluation lead-in part allows patients with any line of prior ALK inhibitor which includes treatment-naïve patients; however, ALK inhibitor-naïve patients may be enrolled after the confirmation of first 3 DLT evaluable patients to have no more than 1 DLT during Cycle 1 by investigator's judgement. The expansion part consists of the TKI-naïve expansion cohort and the refractory expansion part, and the refractory expansion part includes the main cohort and a subcohort based on prior ALK inhibitor treatment. The TKI-naïve expansion cohort includes the patients who have not received any prior TKI including ALK inhibitor. In this cohort, the efficacy will be evaluated, and total of 32 patients will be enrolled. The main cohort of the refractory expansion part includes patients who had previously received alectinib (as their only ALK inhibitor) or both alectinib and crizotinib (regardless the sequence of those 2 ALK inhibitors). The main cohort of the refractory expansion part will be used for the primary analysis of efficacy, and a total of 47 patients will be enrolled in the main cohort of the refractory expansion part. Patients with all other sequences of up to 2 prior ALK inhibitor(s) may be included in the subcohort of the refractory expansion part. Such other ALK inhibitors include (1) crizotinib only, (2) ceritinib only, (3) lorlatinib only, (4) both crizotinib and ceritinib, (5) both alectinib and ceritinib, (6) both crizotinib and lorlatinib, (7) both alectinib and lorlatinib, and (8) both ceritinib and lorlatinib. Up to 20 patients will be enrolled in the subcohort of the refractory expansion part.

In this study, brigatinib will be administered at 90 mg QD for the first 7 days and then 180 mg QD (90 mg QD→180 mg QD). In the safety evaluation lead-in part, patients will be monitored for intensive PK, and the tolerability of 90 mg QD→180 mg QD dosing will be confirmed. If the 90 mg QD→180 mg QD dosing regimen is considered tolerable, additional patients enrolled in the expansion part will be treated with the same dosing schedule (90 mg QD→180 mg QD).

For the TKI-naïve expansion cohort, 32 patients will be enrolled and12 month PFS rate will be evaluated as the primary endpoint. The primary analysis will be performed at around 10 months after the enrollment of the last subject in TKI-naïve expansion cohort. The sample size and evaluation timing may be adjusted based on results of second interim analysis of ALTA-1L study, and actual enrollment period of the TKI-naïve expansion cohort.

For the main cohort of the refractory expansion part, there are 2 stages: the first 29 patients in the main cohort are included in Stage 1, and further patients will be continuously enrolled into Stage 2. An interim analysis for futility and efficacy will be performed in the Stage 1 population when the first 29 post-alectinib patients have had the opportunity to complete at least 3 postbaseline scans (ie, after the Cycle 7 Day 1 disease assessment). Enrollment will not be suspended during evaluation of those 29 patients.

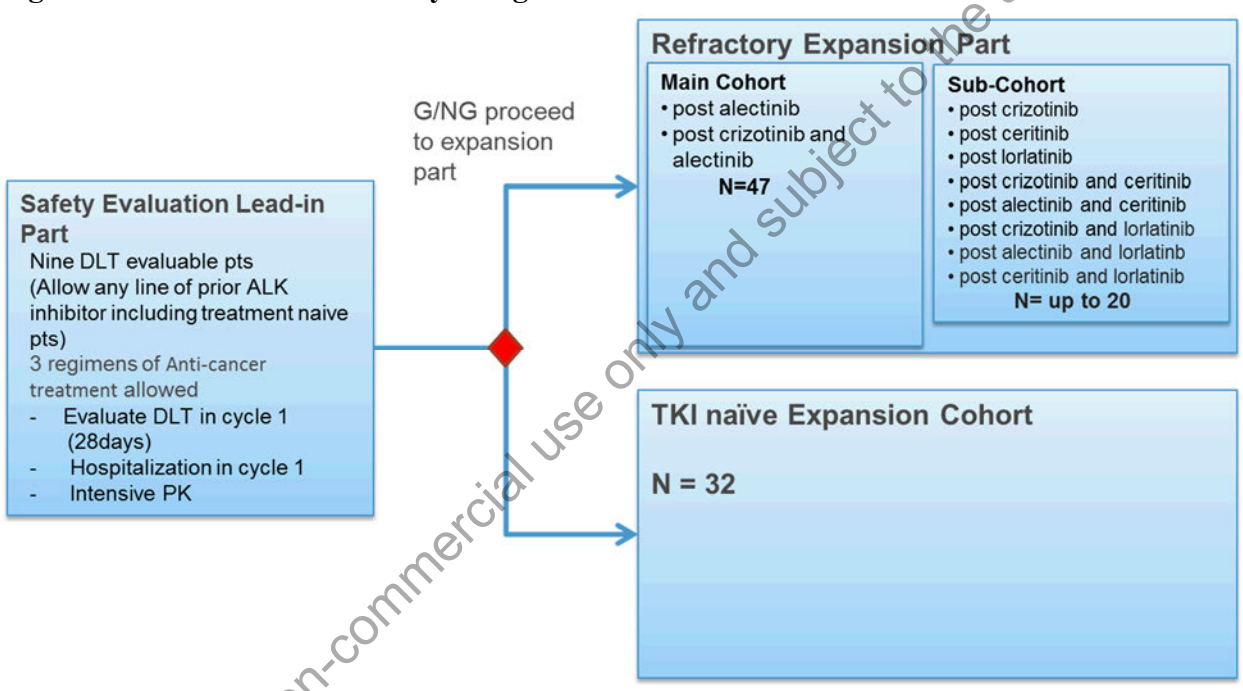
Following the screening period, eligible patients will be enrolled and treated with brigatinib. A patient is considered to be enrolled in the study when the first dose of brigatinib is administered.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.

Response evaluation per RECIST version 1.1 will be done by both the investigator and an IRC. The primary analysis will performed on the results from the IRC.

Patients will be treated until they experience objective progressive disease (PD) per RECIST version 1.1, as assessed by the investigator, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason. Treatment of patients with brigatinib may be continued at the tolerated dose level, despite investigator-assessed PD by RECIST version 1.1, if the patient otherwise has evidence of ongoing clinical benefit. In this case, discussions and agreements between the investigator and the sponsor's project clinician (or designee) are required.

Figure 4.a Overview of Study Design



Safety Evaluation Lead-in Part

Nine DLT-evaluable patients will be enrolled in the safety evaluation lead-in part. The patients in the safety evaluation lead-in part will be hospitalized during Cycle 1 in general, and their condition will be closely monitored for safety and tolerability. Serial blood samples will be collected for the intensive PK profile. If a patient wishes to return home temporarily and the investigator confirms that the patient's symptoms are stable per the available data, then the patient may return home temporarily except on Days 1 through 10 and Days 22 and 23, provided this does not interfere with the study assessments. The investigator must document the confirmation record for stabilization of the patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary leave.

The patients in the safety evaluation lead-in part will receive brigatinib 90 mg QD→180 mg QD. A cycle of therapy comprises 28 days of treatment. If a patient is NOT considered DLT evaluable for any reason, the patient will be replaced.

DLTs are defined in Section 8.2. Tolerability of the 90 mg QD→180 mg QD schedule will be determined on the basis of the DLTs observed in Cycle 1. If a DLT is observed in fewer than 3 of the 9 DLT-evaluable patients in the safety evaluation lead-in part, the 90 mg QD→180 mg QD regimen will be used for the patients enrolled in the expansion part. Further details on the dose expansion rules are described in Section 8.3.

Expansion Part (Refractory Expansion Part and TKI-Naïve Expansion Cohort)

Patients in the refractory expansion part and the TKI-naïve expansion cohort may be managed on an outpatient basis, and the number of study sites will be increased up to approximately 40. Patients in the refractory expansion part and the TKI-naïve expansion cohort will undergo less-intensive PK blood sampling than patients in the safety evaluation lead-in part.

On an outpatient basis, patients will visit the hospital on Days 1, 8, and 15 of Cycle 1, and then on Day 1 of each cycle after Cycle 2. Tumor assessment will be performed every 2 cycles from Cycle 3 Day 1 through Cycle 15 Day 1, then every 3 cycles thereafter until the last dose of study drug. For patients who discontinue study treatment in the absence of PD, additional tumor assessment should continue at the same time points as the study treatment until PD or the start of another systemic anticancer therapy.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoints are:

- Confirmed ORR as assessed by an IRC, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the main cohort of the refractory expansion part
- 12 months PFS rate as assessed by an IRC, per RECIST version 1.1 in the TKI-naïve expansion cohort

5.2 Secondary Endpoints

The secondary endpoints are:

a) Efficacy endpoint in the TKI-naïve expansion cohort, the overall population of the refractory expansion part, and the safety evaluation lead-in part:

– Confirmed ORR, as assessed by an IRC, per RECIST version 1.1.

b) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, the overall population of the refractory expansion part:

– DOR, as assessed by an IRC, per RECIST version 1.1.

– PFS, as assessed by an IRC, per RECIST version 1.1.

- DCR, as assessed by an IRC, per RECIST version 1.1.
- Time to response, as assessed by an IRC, per RECIST version 1.1.
- OS.
- CNS response, as assessed by IRC, per modified RECIST version 1.1 for assessment of intracranial efficacy (Appendix H) (iORR and iDOR in patients who had measurable CNS metastases, and iPFS in all patients).
- Time on treatment.

c) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, and the safety evaluation lead-in part:

- Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.
- PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L (except for the safety evaluation lead-in part).

d) PK endpoint in the safety evaluation lead-in part:

- Brigatinib maximum observed plasma concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC) on Cycle 1 Days 1 and 22.

5.3 Safety Endpoints

The safety endpoints are:

- The number and percentage of patients with TEAEs in the overall population.
- The number and percentage of patients with Grade 3 or higher TEAEs in the overall population.
- The number and percentage of patients with serious TEAEs in the overall population.
- The number and percentage of patients discontinuing study drug because of TEAEs in the overall population.
- The number of patients with DLTs during Cycle 1 in the safety evaluation lead-in part.

5.4 cci [redacted]

cci [redacted]

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The purpose of this phase 2 study is to determine efficacy of brigatinib in patients with ALK-positive NSCLC.

In the safety evaluation lead-in part, 9 DLT-evaluable patients will be enrolled for intensive safety and PK monitoring. This number of patients was derived from the following considerations: The meaningful intensive PK characterization needs to be conducted with more than 6 patients. It is assumed that 9 patients may be reasonable to secure the number of patients needed for intensive PK characterization, even with potential dropouts, and to evaluate the tolerability of the study drug. Also, 9 DLT-evaluable patients is enough to evaluate tolerability before expanding the dose cohort to a larger population using a conventional 3+3 design.

The sample size in the main cohort of the refractory expansion part was determined to allow confirmation that the true ORR (expected response rate) is greater than the threshold response rate of 15% for patients previously treated with alectinib alone and those treated with both alectinib and crizotinib. The rationale for the 15% response rate for the alectinib (with or without crizotinib) pretreated population is based on the consideration that compared with crizotinib, patients who have failed alectinib are less likely to respond to subsequent therapy because of alectinib's greater potency and better coverage of ALK mutations compared with crizotinib.

A sample size of 47 patients in the post-alectinib population of the refractory expansion part with the stopping rule mentioned in Section 13.2 will allow the study to have more than 90% power to rule out a threshold response rate when the true ORR is expected or higher than 35% with a 1-sided alpha of 0.025, according to the H1-minimax design in Englert [16].

The number of patients in the subcohort of the refractory expansion part (ie, patients previously treated with crizotinib only, ceritinib only, lorlatinib only, both crizotinib and ceritinib, both alectinib and ceritinib, both crizotinib and lorlatinib, both alectinib and lorlatinib, or both ceritinib and lorlatinib) will be limited to 20. These patients will be included in evaluations of the overall population.

The sample size in the TKI-naïve expansion cohort was determined to allow confirmation that the true 12 months PFS rate (expected response rate) is greater than the threshold of 42.6% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L Crizotinib arm) for TKI-naïve patients.

A sample size of 32 patients in the TKI-naïve expansion cohort will allow the study to have approximately 80% power to rule out the threshold rate (42.6%) when the true 12 months PFS rate is expected or higher than 66.5% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L Brigatinib arm) with a 1-sided alpha of 0.05, considering 10% patients will discontinue the study follow-up before the 12 months milestone due to reasons other than disease progression assessed by IRC or death, and 8 months enrollment period. The primary

analysis will be performed at around 10 months after the enrollment of the last subject in the TKI-naïve expansion cohort. The sample size and evaluation timing may be adjusted based on results of second interim analysis of ALTA-1L study, and actual enrollment period of the TKI-naïve expansion cohort.

Overall, the total number of patients will be approximately 110 patients.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

A statistical test for the primary endpoint will be reported as 1-sided and will be assessed at α=0.025 significance level and all confidence intervals will be reported as 2-sided unless otherwise stated. P-values will be rounded to 4 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

7.1.1 Study Definitions

How to convert a time-to-event endpoint unit from day to month:

value (Month)= value (Day)/30.4375

Dose intensity:

Total amount of doses taken/(Last non-zero dose date – First dose date +1)

Relative Dose Intensity:

(Total amount of dose taken /Total amount of dose planned per initial dose)*100

Objective Response Rate(ORR):

The proportion of patients who are confirmed to have achieved CR or PR

Confirmed responses

Responses that persist on repeat imaging 4 weeks (allowing a minus 3-day time window) or more after initial response, which will be confirmed by the investigator or IRC.

Duration of Response(DOR):

The time between the first documentation of objective tumor response (CR or PR) and the first subsequent documentation of objective PD or death due to any cause, whichever occurs first

Progression-Free Survival (PFS):

The time from the start of study treatment to the first documentation of objective PD or to death due to any cause, whichever occurs first.

- Based only on radiological assessments verified by an IRC. Clinical progression is not considered a progression endpoint.
- The date of death when the patient is closely followed. However, deaths occurring after two or more missed visits are censored at the last visit
- The detailed scheme of progression and censoring for the primary analysis of PFS is specified in Table 7.a.

Table 7.a The Scheme of Progression and Censoring for PFS

Situation	Date of progression or censoring	Outcome
Documented disease progression or death with no baseline disease assessment	Earliest of the following: Date of death Date of progression	Progressed
New anticancer treatment (including palliative radiotherapy and cancer-related surgery) started prior to documented disease progression or death	Date of last adequate radiological assessment prior to initiation of new anticancer treatment (including palliative radiotherapy and cancer-related surgery)	Censored
Death or PD without more than 1 missing radiographic assessment	Date of death or first PD whichever occurred first	Progressed
Death or PD after two or more missing radiographic assessments	Date of last adequate radiological assessment	Censored
No progression or death	Date of last adequate radiological assessment	Censored

Disease Control Rate (DCR):

The proportion of patients who are confirmed to have achieved CR or PR or have a best overall response of stable disease (SD) for 6 weeks or more after initiation of study drug.

Time to response:

The time interval from the date of the first dose of study treatment until the initial observation of CR or PR for patients with confirmed CR/PR.

Overall Survival (OS):

The time from the start of study treatment to the date of death.

Best response in target lesions:

The maximum unsigned decrease (or the minimum increase if no decrease) in percentage in the sum of the longest dimensions of the target lesions at a single assessment as compared with baseline.

Time on treatment

Time on treatment is defined as the time interval from the first dose to the last dose of assigned study treatment.

ILD/Pneumonitis Events:

The search strategy included manual selection of PTs of Interstitial lung disease and Pneumonitis.

Bradycardia Events:

The search strategy included manual selection of PTs of Ibradycardia, Central bradycardia, Heart rate decreased, Sinus bradycardia, Bradyarrhythmia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree and Atrioventricular block second degree.

Hypertension Events:

The search strategy included manual selection of PTs of Accelerated hypertension, Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic increased, Diastolic hypertension, Hypertension and Systolic hypertension.

GI Events:

Some PTs were retrieved manualy from SMQ; Gastrointestinal nonspecific symptoms and therapeutic procedures. For other GI events, the search strategy included manual selection of PTs of Dysphagia, Gastrointestinal tract irritation, Regurgitation, Retching and Vomiting projectile. Further details are given in Appendix 2.

Increased Insulin/ Hyperglycemia Events:

Hyperglycemia Events: The search strategy included manual selection of PTs of Blood glucose increased, Diabetes mellitus, Glycosylated haemoglobin increased, Hyperglycaemia, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus and Type 3 diabetes mellitus.

Increased Insulin Events: The search strategy included manual selection of PTs of Blood Insulin increased and Hyperinsulinaemia.

Hyperglycemia Events and Increased Insulin Events were analyzed and tabulated together.

Hepatic Events

Some PTs were retrieved manualy from SMQ; Liver related investigations, signs and symptoms, Cholestasis and jaundice of hepatic origin, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions and Hepatitis, non-infectious. Further details are given in Appendix 2.

Elevated CPK

The search strategy included manual selection of PTs of Blood creatine increased, Blood creatine phosphokinase increased, Hypercreatinaemia, Blood creatine phosphokinase MB increased, Blood creatine phosphokinase MM increased and Blood creatine phosphokinase BB increased.

Muscle Toxicity

The search strategy included manual selection of PTs of Muscle necrosis, Myoglobin blood increased, Myoglobin blood present, Myoglobin urine present, Myoglobinaemia, Myoglobinuria, Myopathy, Myopathy toxic, Necrotising myositis, Rhabdomyolysis, Biopsy muscle abnormal, Muscle discomfort, Muscle disorder, Muscle fatigue, Muscular weakness, Musculoskeletal discomfort, Musculoskeletal disorder, Musculoskeletal pain, Myalgia, Myositis and Musculoskeletal chest pain.

Pancreatic Events

Chemical Pancreatitis: The search strategy included manual selection of PTs of Amylase abnormal, Amylase increased, Hyperamylasaemia, Hyperlipasaemia, Lipase abnormal, Lipase increased, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased and Ultrasound pancreas abnormal.

Clinical Pancreatitis: The search strategy included manual selection of PTs of Haemorrhagic necrotic pancreatitis, Ischaemic pancreatitis, Oedematous pancreatitis, Pancreatic abscess, Pancreatic haemorrhage, Pancreatic necrosis, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising and Pancreatitis relapsing.

Chemical and clinical pancreatic events were analyzed and tabulated together.

Peripheral Neuropathy Events

A broad search strategy was used for the retrieval of all active PTs from the SMQ: Peripheral neuropathy.

Skin and Subcutaneous Events

The search strategy was used for the retrieval of all active PTs from the SOC; Skin and Subcutaneous Events.

Visual Impairment Events

The search strategy was used for the retrieval of all active PTs from the HLGT; vision disorder, some PTs were retrieved from SMQs; retinal disorder, glaucoma, lens disorder. For other Visual Impairment events, the search strategy included manual selection of PTs. Further details are given in Appendix 2.

Photosensitivity

The search strategy was used for the retrieval of all active PTs from the HLT; photosensitivity and photodermatosis conditions. Further details are given in Appendix 2.

CNS involvement at Screening:

The subjects with Brain and Leptomeningeal Involvement at Screening

Treatment-Emergent Adverse Events leading to study drug dose modification:

TEAE leading to dose discontinuation, dose interruption, or dose reduction

The subject who administrated any Chemo therapy:

The subjects who administrated the medication whose code are matched in the following table as prior anticancer therapy

Bevacizumab
Carboplatin
Chemotherapeutics
Cisplatin
Docetaxel
Gimeracil;Oteracil potassium;Tegafur
Gimeracil;Oteracil;Tegafur
Motesanib
Nivolumab
Paclitaxel
Pembrolizumab
Pemetrexed disodium
Tegafur;Uracil
Vinorelbine tartrate

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Day to the scheduled Day will be used. If there are two observations equidistant to the scheduled Day, the later observation will be used.

HRQOL scores(EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L), 12-lead ECG, ECOG performance status, and Testosterone

Visit	Scheduled Day (days)	Time Interval (days)	
		Day*	Follow-up Day
Baseline	Day from first visit in cycle1:	1	-14 - 1
Cycle 2	Day from first visit in cycle2:	1	-3 - 29
Cycle 3	Day from first visit in cycle3:	1	-3 - 29
Cycle 4	Day from first visit in cycle4:	1	-3 - 29
Cycle 5	Day from first visit in cycle5:	1	-3 - 29
Cycle 6 and beyond	Day from first visit in each cycle:	1	-3 - 29

* "Day" indicates day after first visit in cycle which is mentioned in "Scheduled Study Day".
If the data is in the scope of several visits, the data will be regarded as the candidate data of the latest visit.

Laboratory Assessments except HbA1c and Testosterone

Visit	Scheduled Day (days)	Time Interval (days)	
		Day*	Follow-up Day
Baseline	Day from first visit in cycle1:	1	-14 - 1
Cycle 1 Day15	Day from first visit in cycle1:	15	2 - 29
Cycle 2	Day from first visit in cycle2:	1	-3 - 29
Cycle 3	Day from first visit in cycle3:	1	-3 - 29
Cycle 4	Day from first visit in cycle4:	1	-3 - 29
Cycle 5	Day from first visit in cycle5:	1	-3 - 29
Cycle 6 and beyond	Day from first visit in each cycle:	1	-3 - 29

* "Day" indicates day after first visit in cycle which is mentioned in "Scheduled Study Day".
If the data is in the scope of several visits, the data will be regarded as the candidate data of the latest visit.

Vital signs

Visit	Scheduled Day (days)	Time Interval (days)	
		Day*	Follow-up Day
Baseline	Day from first visit in cycle1:	1	-14 - 1
Cycle 1 Day8	Day from first visit in cycle1:	8	2 - 11
Cycle 1 Day15	Day from first visit in cycle1:	15	12 - 29
Cycle 2	Day from first visit in cycle2:	1	-3 - 29
Cycle 3	Day from first visit in cycle3:	1	-3 - 29
Cycle 4	Day from first visit in cycle4:	1	-3 - 29
Cycle 5	Day from first visit in cycle5:	1	-3 - 29
Cycle 6 and beyond	Day from first visit in each cycle:	1	-3 - 29

* "Day" indicates day after first visit in cycle which is mentioned in "Scheduled Study Day".
If the data is in the scope of several visits, the data will be regarded as the candidate data of the latest visit.

HbA1c

Visit	Scheduled Day (days)	Time Interval (days)	
		Day*	Follow-up Day
Baseline	Day from first visit in cycle1:	1	-14 - 1
Cycle 4 and beyond	Day from first visit in each cycle:	1	-3 - 29

* "Day" indicates day after first visit in cycle which is mentioned in "Scheduled Study Day".
If the data is in the scope of several visits, the data will be regarded as the candidate data of the latest visit.

7.1.4 Methods for Handling Missing Data and Specific Data

All available efficacy and safety data will be included in data listing and tabulations. No imputation of values for missing data will be performed unless otherwise specified.

- For ORR as assessed by an IRC, if any tumor response of post baseline is not assessed or any tumor response of baseline is not confirmed as measurable disease per the IRC, the patients will be treated as the one who are not confirmed to have achieved CR or PR
- For ORR as assessed by an investigator, if any tumor response of post baseline is not assessed or any tumor response of baseline is not confirmed as measurable disease per the investigator, the patients will be treated as the one who are not confirmed to have achieved CR or PR
- For DCR, patients with only non-measurable disease who had a CR or non-CR/non-PD will be considered as having achieved DCR.
- For DOR, if tumor response cannot be confirmed, the patient will not be analyzed.
- For EORTC QLQ-C30, QLQ-LC13, published scoring manuals and guidelines will be used to calculate scores and handle missing data.
- For stage at Screening, if no data has been input in CRF, the stage at initial diagnosis will be used as the stage at screening,
- For clinical laboratory tests, values less than the lower limit of quantification will be treated as value of lower limit when calculating the descriptive statistics.
- Disease duration with first diagnosis date of ALK + non small cell lung cancer that are completely or partially missing will be derived as follows:
  - If the year is missing, then the disease duration will be treated as missing.
  - If the year is present but the month is missing, then the month will be treated as January for the calculation.

7.2 Analysis Sets

The refractory expansion part and safety evaluation lead-in part:

Safety population will be defined as patients who receive at least 1 dose of study drug will be used for all safety analyses.

Full analysis set (FAS) population will be defined as all patients who receive at least 1 dose of study drug.

FAS-P population, the main analysis set used for primary efficacy analysis, will be defined a subset of the FAS population consisting of first 47 patients in the main cohort of the expansion part.

Per-protocol (PP) population will be defined as a subset of the FAS-P population including patients who do not have a major protocol violation listed below:

- Subjects who did not meet inclusion criteria #3, #4, #6 or, #10.
- Subjects who met exclusion criteria #9, #10, #11, #13 or, #14.
- Subjects who have violated the following rules specified in section 8.5.
  - Any other systemic anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS and WBRT, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Hormonal contraception is allowed.
  - Use of any other investigational drug or device.
  - Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

PK population will be defined as patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist

DLT population will be a subset of the DLT evaluable subject who completes at least 75% of planned cumulative doses in safety evaluation lead-in part.

The TKI-naïve expansion cohort:

Safety population will be defined as patients who receive at least 1 dose of study drug will be used for all safety analyses.

Full analysis set (FAS) population will be defined as all patients who receive at least 1 dose of study drug.

PK population will be defined as patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist

Per-protocol (PP) population will be defined as a subset of the FAS population including patients who do not have a major protocol violation listed below:

- Subjects who did not meet inclusion criteria #3, #4, #6 or, #10.

- Subjects who met exclusion criteria #1, #9, #10, #11, #13 or, #14.
- Subjects who have violated the following rules specified in section 8.5.
  - Any other systemic anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS and WBRT, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Hormonal contraception is allowed.
  - Use of any other investigational drug or device.
  - Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s):
- Date First Subject Signed Informed Consent Form
- Date of Last Subject's Last Visit
- MedDRA Version
- WHO Drug Version
- SAS Version Used for Creating the Datasets

Analytical Method(s):

(1) Study Information
Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set: All Subjects Who Did Not Enter the Treatment Period

Analysis Variable(s):

Age (years)	[20<= - <65, 65<= - <=Max]
	[20<= - <50, 50<= - <65, 65<= - <75,75<= - <=Max]
Gender	[Male, Female]

Analytical Method(s) :

(1) Screen Failures
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s) :

Eligibility Status	[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]
Primary Reason for Subject Not Being Eligible	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) :

(1) Eligibility for Entrance into the Treatment Period
Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s) :

Status of Entrance into the Treatment Period	[Entered]

Stratum: Site — [Site name and number will be used as categories]

Analytical Method(s) :

(1) Number of Subjects Who Entered the Treatment Period by Site
Frequency distribution will be provided for each stratum.

7.3.5 Disposition of Subjects

Analysis Set: All Subjects Who Entered the Treatment Period

All Subjects Who Entered the Treatment Period in the main cohort

Analysis Variable(s) :

Subject Status(End of Treatment)	[Completed, Adverse Event, Death, Lost to Follow-up, Progressive Disease, Protocol Deviation, Study Terminated by Sponsor, Symptomatic Deterioration, Withdrawal by Subject, Other, Ongoing]
Subject Status(Follow-up)	[Death, Lost to Follow-up, Study Terminated by Sponsor, Withdrawal by Subject, Other, Ongoing]

Analytical Method(s) :

(1) Disposition of Subjects
Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

7.3.6 Protocol Deviations

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s) :

Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol(Primary Endpoint or Safety Related), Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s) :

(1) Protocol Deviations
Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.7 Analysis Sets

Analysis Set: All Subjects Who Entered the Treatment Period

All Subjects Who Entered the Treatment Period in the main cohort

(For the refractory patients)

All Subjects Who Entered the Treatment Period in the safety evaluation lead-in part.(For the refractory patients)

Analysis Variable(s) :

Handling of Subjects	[Categories are based on Subject Evaluability List]
Analysis Sets	
Full Analysis Set	[Included]
Full Analysis Set P (For the refractory patients)	[Included]
Per Protocol Set	[Included]
Safety Analysis Set	[Included]
PK population	[Included]
DLT population (For the refractory patients)	[Included]

Analytical Method(s) :

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

For DLT population, frequency distributions will be provided for the subjects in the safety evaluation lead-in part. For other populations, it will be done in overall population and main cohort. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category for each analysis set. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

For analysis on Full Analysis Set P, all subjects who entered the treatment period in the main cohort will be used as analysis set.

7.4 Demographic and Other Baseline Characteristics

Analysis Set: Safety analysis set

Full Analysis Set

Full Analysis Set P(For the refractory patients)

Analysis Variable(s) :		
	Age (years)	[20<= - <65, 65<= - <=Max]
		[20<= - <50, 50<= - <65, 65<= - <75,75<= - <=Max]
	Gender	[Male, Female]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) at Baseline	[Min<= - <50, 50<= - <60, 60<= - <70, 70<= - <80, 80<= - <=Max]
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	Stage at Initial Diagnosis	[IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, Unknown or not staged]
	Stage at Screening	[IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, Unknown or not staged, Refractory, Other]
	Histopathological Classification of NSCLC	[Adenocarcinoma, Adenosquamous carcinoma, Large cell, Squamous, Unknown, Other]
	Lung involvement at Screening	[Left Lung, Right Lung, Both Lungs, Lungs not involved]
	CNS involvement at Screening	[Yes, No]
	Time from Initial Diagnosis to study treatment (months)	
	ECOG Performance Status	[0, 1, 2, 3, 4]
	Was the genetic status of ALK in tumor tissue assessed?	[Yes, No]
	ALK mutation method of assessment	
	FISH-Vysis	[Yes]
	FISH-non Vysis	[Yes]

Vysis ALK Break Apart FISH Probe Kit	[Yes]
Nichirei Histofine RALK iAEP Kit	[Yes]
Ventana ALK (D5F3) CDx Assay	[Yes]
RT-PCR	[Yes]
Sequencing	[Yes]
Unknown	[Yes]
Other	[Yes]
	[Yes]
Was an abnormality detected?	[Yes, No, Unknown]
fusion partner	[EML4, TFG, KIF5B, NPM, Fusion partner unknown, Other fusion partner]
ALK secondary mutation	
T1151Tins	[Yes]
L1152R	[Yes]
C1156Y	[Yes]
I1171T	[Yes]
I1171N	[Yes]
I1171S	[Yes]
F1174C	[Yes]
F1174L	[Yes]
V1180L	[Yes]
L1196M	[Yes]
L1198F	[Yes]
G1202R	[Yes]
G1202del	[Yes]
D1203N	[Yes]
S1206Y	[Yes]

E1210K	[Yes]
G1269A	[Yes]
Unknown	[Yes]
Other	[Yes]
Any Anticancer Therapies	[Yes, No]
Regimen	[Alectinib only, Crizotinib and Alectinib, Crizotinib only, Ceritinib only, Lorlatinib only, Crizotinib and Ceritinib, Alectinib and Ceritinib, Crizotinib and Lorlatinib, Alectinib and Lorlatinib, Ceritinib and Lorlatinib, Other]
Any Prior Chemo therapy	[Yes, No]
Any Prior Radiotherapy	[Yes, No]
Anatomic Site	
Lung	[Yes]
Mediastinal Lymph Nodes	[Yes]
Bone	[Yes]
Brain	[Yes]
Other	[Yes]

Analytical Method(s) :

(1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Medical History

Concurrent Medical Conditions

Analytical Method(s) :

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Medication History

Concomitant Medications

Analytical Method(s) :

(1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Safety Analysis Set in the main cohort

Analysis Variable(s) :

Number of treated cycle [0, 1, 2, 3, 4, 5, 6<= - <=Max]

Total amount of doses taken (mg)

Dose intensity (mg/day)

Relative dose intensity (%)

Duration of treatment (month)

Duration of follow-up (month)

Analytical Method(s) :

(1) Study Drug Exposure and Compliance
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Full Analysis Set P(For the refractory patients)

Full Analysis Set (For TKI-naïve Patients)

Analysis Variable(s):

Confirmed ORR as assessed by an IRC(For the refractory patients)

PFS as assessed by an IRC (For TKI-naïve Patients)

Analytical Method(s):

The point estimate and its 2-sided 95% confidence interval will be summarized. The point estimate will be calculated by the method suggested by Kunzmann(2017) with weight function of uniform distribution of [0,1], which means that the point estimate will ((x1+x2+1)/49)x100. X1 and x2 represents the number of events at IA for the first 29 patients in the main cohort and the number of events at PA for the last 18 patients in the main cohort, respectively.

The confidence interval will be done based on the Clopper-Pearson type.

For PFS, the rate at 12 and, 24 months and the associated two-sided 90% confidence intervals with complementary log-log link will also be provided using the Kaplan-Meier method.

7.8.1.2 Secondary Analysis

Analysis Set: Per Protocol Set(For the refractory patients)

Analysis Variable(s): Confirmed ORR as assessed by an IRC

PFS as assessed by an IRC (For TKI-naïve Patients)

Analytical Method(s): The point estimate and its 2-sided 95% confidence interval will be summarized. The point estimate will be calculated based on maximum likelihood estimation. The confidence interval will be done based on the Clopper-Pearson type.

For PFS, the rate at 12 and, 24 months and the associated two-sided 90% confidence intervals with complementary log-log link will also be provided using the Kaplan-Meier method.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Confirmed ORR by the investigator

Analysis Set: Full Analysis Set P(For the refractory patients)

Analysis Variable(s): Confirmed ORR as assessed by the investigator

Analytical Method(s): The point estimate and its 2-sided 95% confidence interval will be summarized. The point estimate will be calculated based on maximum likelihood estimation. The confidence interval will be done based on the Clopper-Pearson type.

7.8.2.2 Confirmed ORR by an IRC

Analysis Set: Full Analysis Set

Full Analysis Set P(For the refractory patients)

Analysis Variable(s): Confirmed ORR as assessed by an IRC

Analytical Method(s):

The point estimate and its 2-sided 95% confidence interval will be summarized. The point estimate will be calculated based on maximum likelihood estimation. The confidence interval will be done based on the Clopper-Pearson type.

7.8.2.3 Other assessment by an IRC

Analysis Set: Full Analysis Set

Full Analysis Set P(For the refractory patients)

Patients who had measurable CNS metastases in Full Analysis Set

Patients who had measurable CNS metastases in Full Analysis Set P

(For the refractory patients)

Analysis Variable(s):

DOR as assessed by an IRC

PFS as assessed by an IRC(For the refractory patients)

DCR as assessed by an IRC

Time to response as assessed by an IRC

OS

CNS response

iORR by an IRC

iDOR by an IRC

iPFS by an IRC

Time to intracranial response as assessed by an IRC

Time on treatment

Best response in target lesions

Analytical Method(s):

For iDOR and DOR, the cumulative incidences and the two-sided 95% confidence intervals will be provided using the Kaplan-Meier method. For DOR, Time to response, and Time to intracranial response as assessed by an IRC, summary of descriptive analysis will be provided for subjects with confirmed CR or PR.

For Time on treatment, the summary of descriptive analysis will be provided and swimmer's plot will be presented.

For iPFS, PFS, and OS, the rate at 12 and, 24 months and the associated two-sided 95% confidence intervals with complementary log-log link will also be provided using the Kaplan-Meier method.

Especially, for iPFS, considering the progression by investigator assessment as competing risk and only intracranial progression by IRC as event, the cumulative incidence function for event will be provided.

Additionally, for the analysis for TKI-naïve patients, the same analysis mentioned above will be performed in Per Protocol Set.

For iORR, DCR, CNS response, the point estimate and its 2-sided 95% confidence interval will be summarized. The point estimate will be calculated based on maximum likelihood estimation. The confidence interval will be done based on the Clopper-Pearson type.

For iDOR and iORR, patients who had measurable CNS metastases in Full Analysis Set or in Full Analysis Set P will be used as analysis set.

For best response in target lesions, summary of descriptive analysis will be provided with a waterfall plot.

7.8.2.4 EORTC QLQ-C30

Analysis Set: Full Analysis Set in expansion part

Full Analysis Set P (For the refractory patients)

Analysis Variable(s):

Global health status

Global health status

Functional scales

Physical functioning

Role functioning

Emotional functioning

Cognitive functioning

Social functioning

Symptom scales

Fatigue

Nausea and vomiting

Pain

Dyspnoea

Insomnia

Appetite loss

Constipation

Diarrhoea

Financial difficulties

Visit: Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18

Analytical Method(s): Descriptive statistics for observed values for each visit and changes from baseline will be provided.

7.8.2.5 EORTC QLQ-LC13

Analysis Set: Full Analysis Set in expansion part

Full Analysis Set P(For the refractory patients)

Analysis Variable(s): Dyspnoea

Coughing

Haemoptysis

Sore mouth

Dysphagia

Peripheral neuropathy

Alopecia

Pain in chest

Pain in arm or shoulder

Pain in other parts

Visit: Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18

Analytical Method(s): Descriptive statistics for observed values for each visit and changes from baseline will be provided.

7.8.2.6 EQ-5D-5L

Analysis Set: Full Analysis Set in expansion part

Full Analysis Set P(For the refractory patients)

Analysis Variable(s): Mobility

Selfcare

Activity

Pain

Anxiety

EQ_VAS

Index Value

Visit: Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18

Analytical Method(s): For categorical variables, frequency distributions for each visit will be provided. And for continuous variables, descriptive statistics for observed values for each visit and changes from baseline will be provided.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Confirmed ORR by an IRC by the previous ALK inhibitor regimen

Analysis Set: Full Analysis Set

Full Analysis Set-P(For the refractory patients)

Analysis Variable(s): Confirmed ORR as assessed by an IRC (For the refractory patients)

PFS as assessed by an IRC (For TKI-naïve Patients)

Stratified

Variable(s):	Age (years)	[20<= - <65, 65<= - <=Max]
	Gender	[Male, Female]
	CNS involvement at Screening	[Yes, No]
	Previous ALK Inhibitor Regimen (For the refractory patients)	[Alectinib only, Crizotinib and Alectinib, Crizotinib only, Ceritinib only, Lorlatinib only, Crizotinib and Ceritinib, Alectinib and Ceritinib, Other]
	ALK secondary mutation	[Containing G1202R, Not containing G1202R but containing other, No or unknown somatic mutation]
	Any Prior Chemo Therapy	[Yes, No]
Analytical Method(s):	The point estimate and its 2-sided 95% confidence interval will be summarized by stratified variable. The point estimate will be calculated based on maximum likelihood estimation. The confidence interval will be done based on the Clopper-Pearson type. For PFS, the rate at 12 and, 24 months and the associated two-sided 90% confidence intervals with complementary log-log link will also be provided using the Kaplan-Meier method by stratified variable.	

7.8.3.2 Proportion of patients with event

Analysis Set:	Full Analysis Set P (For the refractory patients) Full Analysis Set
Analysis Variable(s):	Proportion of patients with PFS event Proportion of patients with iPFS event (For the naive patients) Proportion of patients with OS event Proportion of patients with DOR event

Analytical Method(s): The point estimate and its 2-sided 95% confidence interval will be summarized. The confidence interval will be done based on the Clopper-Pearson type.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma concentrations of brigatinib and AP26123

Analysis Set: PK population

Analysis Variable(s): Plasma concentrations of brigatinib and AP26123

Time Point: (Safety Evaluation Lead-in Part)

Visit: Cycle 1 Day 1 and Cycle 1 Day 22

Predose and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose (relative to start time of morning dose at Day 1 or 22)

Visit: Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1

Predose

(Expansion Part)

Visit: Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15

Predose and 1-4 hours postdose (relative to start time of morning dose at Day 1, 8, or 15)

Visit: Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1

Predose

Analytical Method(s):

The following summaries will be provided for each analyte by analysis set.

(1) Descriptive statistics (mean, standard deviation, minimum, median and maximum) for observed values will be provided for each time point by dose. In addition, %CV, geometric mean, and geometric %CV will be provided

(2) Observed values will be plotted using individual case plot

(3) Mean of plasma concentrations will be plotted by time point using linear scale.

(4) Mean of plasma concentrations will be plotted by time point using common log scale.

7.9.1.2 Plasma PK parameters of brigatinib and AP26123

Analysis Set: PK population

Analysis Variable(s):

Plasma Concentrations of brigatinib and AP26123

[Cycle 1 Day 1]

Cmax	tmax	AUClast
AUC24	C24	tlast

[Cycle 1 Day 22]

Cmax	tmax	C24
AUC24	AUClast	R(AUC24)
R(Cmax)	CL/F	tlast

Visit: Cycle 1 Day 1 and Cycle 1 Day 22 (Safety Evaluation Lead-in Part)

Analytical Method(s):

The following summaries will be provided for each analyte by visit.

(1) Descriptive statistics (mean, standard deviation, minimum, median and maximum) for PK parameters will be provided. In addition, geometric mean, 1st and 3rd quartiles, %CV, and geometric %CV will be computed for all PK parameters.

7.9.2 Pharmacodynamic Analysis

Not applicable

7.10 Other Outcomes

Not applicable

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): Treatment-emergent adverse event (TEAE)

Categories: Relationship to Study Drug [Related, Not Related]

Analytical Method(s): The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Drug-related Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
3) Grade 3 or higher Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Grade 3 or higher Drug-RelatedTreatment-Emergent Adverse Events (number of events, number and percentage of subjects)
5) Treatment-Emergent Adverse Events leading to study drug dose modification (number of events, number and percentage of subjects)
6) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
7) Treatment-Emergent Adverse Events leading to study drug interruptions (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events leading to study drug reduction (number of events, number and percentage of subjects)

9) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

10) Drug-Related serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

11) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

12) Drug-RelatedTreatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2), 9), and 11)

  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) will be counted once in the Related category.

- Summary for 3) and 4)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum grade.

- Summaries other than 2), 3), 4), 9) and, 11)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.11.1.2 Frequency of patients with DLTs during Cycle 1 in the safety evaluation lead-in part.

Analysis Set: DLT population (For the refractory patients)

Analysis Variable(s) : Patients with DLTs during Cycle 1 [Yes, No]

Analytical Method(s) : Frequency distributions for categorical variables will be provided.

7.11.1.3 Displays of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s) : TEAE

Categories:

Time of Onset (day)	[1<= - <=28, 29<= - <=56, 57<= - <=84, 85<= - <=112, 113<= - <=140, 141<= - <=168, 169<= - <=Max]
Time of Onset for ILD/Pneumonitis Treatment-Emergent Adverse Events (day)	[1<= - <=14, 15<= - <=Max]

Analytical Method(s) :

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to study drug modification by System Organ Class and Preferred Term

(8) Drug-Related Treatment-Emergent Adverse Events Leading to study drug modification by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events leading to study drug dose discontinuation by System Organ Class and Preferred Term

(10) Drug-Related Treatment-Emergent Adverse Events Leading to study drug discontinuation by System Organ Class and Preferred

Term

(11) Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(12) Drug-Related Treatment-Emergent Adverse Events Leading to study drug interruptions by System Organ Class and Preferred Term

(13) Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(14) Drug-Related Treatment-Emergent Adverse Events Leading to study drug reduction by System Organ Class and Preferred Term

(15) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(16) Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(17) Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(18) Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(19) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(20) ILD/Pneumonitis Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(21) ILD/Pneumonitis Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(22) ILD/Pneumonitis Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(23) ILD/Pneumonitis Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(24) ILD/Pneumonitis Grade 3 or higher Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(25) ILD/Pneumonitis serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(26) ILD/Pneumonitis serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(27) ILD/Pneumonitis Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(28) ILD/Pneumonitis Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(29) ILD/Pneumonitis Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(30) ILD/Pneumonitis Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(31) ILD/Pneumonitis Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(32) ILD/Pneumonitis Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(33) ILD/Pneumonitis Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(34) Hypertension Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(35) Hypertension Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(36) Hypertension Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(37) Hypertension Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(38) Hypertension serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(39) Hypertension serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(40) Hypertension Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(41) Hypertension Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(42) Hypertension Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(43) Hypertension Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(44) Hypertension Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(45) Hypertension Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(46) Hypertension Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(47) Bradycardia Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(48) Bradycardia Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(49) Bradycardia Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(50) Bradycardia Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(51) Bradycardia serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(52) Bradycardia serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(53) Bradycardia Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(54) Bradycardia Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(55) Bradycardia Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(56) Bradycardia Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(57) Bradycardia Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(58) Bradycardia Treatment-Emergent Adverse Events resulting in

death by System Organ Class and Preferred Term

(59) Bradycardia Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(60) GI Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(61) GI Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(62) GI Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(63) GI Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(64) GI serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(65) GI serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(66) GI Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(67) GI Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(68) GI Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(69) GI Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(70) GI Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(71) GI Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(72) GI Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(73) Pancreatic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(74) Pancreatic Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(75) Pancreatic Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(76) Pancreatic Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(77) Pancreatic serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(78) Pancreatic serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(79) Pancreatic Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(80) Pancreatic Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(81) Pancreatic Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(82) Pancreatic Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(83) Pancreatic Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(84) Pancreatic Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(85) Pancreatic Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(86) Increased Insulin/Hyperglycemia Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(87) Increased Insulin/Hyperglycemia Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(88) Increased Insulin/Hyperglycemia Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(89) Increased Insulin/Hyperglycemia Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(90) Increased Insulin/Hyperglycemia serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(91) Increased Insulin/Hyperglycemia serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred

Term

(92) Increased Insulin/Hyperglycemia Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(93) Increased Insulin/Hyperglycemia Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(94) Increased Insulin/Hyperglycemia Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(95) Increased Insulin/Hyperglycemia Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(96) Increased Insulin/Hyperglycemia Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(97) Increased Insulin/Hyperglycemia Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(98) Increased Insulin/Hyperglycemia Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(99) Hepatic Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(100) Hepatic Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(101) Hepatic Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(102) Hepatic Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(103) Hepatic serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(104) Hepatic serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(105) Hepatic Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(106) Hepatic Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(107) Hepatic Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(108) Hepatic Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(109) Hepatic Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(110) Hepatic Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(111) Hepatic Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(112) Elevated CPK Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(113) Elevated CPK Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(114) Elevated CPK Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(115) Elevated CPK Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(116) Elevated CPK serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(117) Elevated CPK serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(118) Elevated CPK Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(119) Elevated CPK Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(120) Elevated CPK Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(121) Elevated CPK Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred

Term

(122) Elevated CPK Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(123) Elevated CPK Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(124) Elevated CPK Drug-Related Treatment-Emergent Adverse Events resulting in death by System Organ Class and Preferred Term

(125) Visual Impairment Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(126) Visual Impairment Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(127) Visual Impairment Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(128) Visual Impairment Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(129) Visual Impairment serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(130) Visual Impairment serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(131) Visual Impairment Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(132) Visual Impairment Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(133) Visual Impairment Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(134) Visual Impairment Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(135) Visual Impairment Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(136) Muscle Toxicity Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(137) Muscle Toxicity Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(138) Muscle Toxicity Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(139) Muscle Toxicity Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(140) Muscle Toxicity serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(141) Muscle Toxicity serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(142) Muscle Toxicity Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(143) Muscle Toxicity Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(144) Muscle Toxicity Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(145) Muscle Toxicity Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(146) Muscle Toxicity Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(147) Peripheral Neuropathy Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(148) Peripheral Neuropathy Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(149) Peripheral Neuropathy Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(150) Peripheral Neuropathy Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(151) Peripheral Neuropathy serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(152) Peripheral Neuropathy serious Drug-Related Treatment-Emergent

Adverse Events by System Organ Class and Preferred Term

(153) Peripheral Neuropathy Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(154) Peripheral Neuropathy Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(155) Peripheral Neuropathy Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(156) Peripheral Neuropathy Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(157) Peripheral Neuropathy Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(158) Skin and Subcutaneous Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(159) Skin and Subcutaneous Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(160) Skin and Subcutaneous Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(161) Skin and Subcutaneous Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(162) Skin and Subcutaneous serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(163) Skin and Subcutaneous serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(164) Skin and Subcutaneous Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(165) Skin and Subcutaneous Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(166) Skin and Subcutaneous Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and

Preferred Term

(167) Skin and Subcutaneous Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(168) Skin and Subcutaneous Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(169) Photosensitivity Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(170) Photosensitivity Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(171) Photosensitivity Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(172) Photosensitivity Drug-Related Grade 3 or higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(173) Photosensitivity serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(174) Photosensitivity serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(175) Photosensitivity Grade 3 or higher serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(176) Photosensitivity Grade 3 or higher serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(177) Photosensitivity Treatment-Emergent Adverse Events leading to study drug discontinuation by System Organ Class and Preferred Term

(178) Photosensitivity Treatment-Emergent Adverse Events leading to study drug interruptions by System Organ Class and Preferred Term

(179) Photosensitivity Treatment-Emergent Adverse Events leading to study drug reduction by System Organ Class and Preferred Term

(180) Most commonly reported Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(181) Most commonly reported Grade 3 or higher Treatment-Emergent

Adverse Events by System Organ Class and Preferred Term

(182) Most commonly reported Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than the CTCAE grade, (19), and (21)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for the CTCAE grade

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (19) and (21)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
  When calculating percentages for each time interval, the number of subjects at risk (ie, subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

- Summary table for (180) and (181)

  Most commonly reported TEAEs refer to PTs whose percentages are at least 10.0% in any one of the treatment groups.

- Summary table for (182)

  Most commonly reported Non-Serious TEAEs refer to PTs whose percentages are at least 5.0% in any one of the treatment groups. If no Non-Serious TEAEs exceed a frequency of 5.0%, the frequency cutoff of 2.0% will be used instead. Percentages will be based on the number of subjects in the safety analysis set.

7.11.1.4 Time to Onset and the Duration of Special Interest Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Time to initial onset of ILD/Pneumonitis

Time to initial onset of Bradycardia Even

Time to initial onset of Hypertension Eve

Time to initial onset of GI Events

Time to initial onset of Pancreatic Events

Time to initial onset of Increased Insulin/Hyperglycemia Events

Time to initial onset of Hepatic Events

Time to initial onset of Elevated CPK Events

Time to initial onset of Visual Impairment Events

Time to initial onset of Muscle Toxicity Events

Time to initial onset of Peripheral Neuropathy Events

Time to initial onset of Skin and Subcutaneous Events

Time to initial onset of Photosensitivity Events

Analytical Method(s) :

For each variable, descriptive statistics will be provided.

7.11.1.5 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s) :

Pretreatment event (PTE)

Analytical Method(s) :

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred

Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology

Hematocrit	Platelet count	Hemoglobin
White blood cell count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes)		

Serum Chemistry

Albumin	Alkaline phosphatase (ALP)	Amylase
ALT	AST	Blood urea nitrogen (BUN)
Calcium	Creatine Phosphokinase (CPK)	Bicarbonate (or total carbon dioxide)
Chloride	Creatinine	Glucose (fasted)
Lactate dehydrogenase (LDH)	C-reactive protein (CRP)	Magnesium
Phosphorus	Potassium	Sodium
Bilirubin (total bilirubin, conjugated and unconjugated bilirubin)		
Protein (total protein)	Uric acid	HbA1c
Insulin	Testosterone (Male Patients Only)	Lipase

Visit: Baseline, Cycle 1 Day 15, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18 (except HbA1c and

Testosterone)

Baseline, Cycle 4, Cycle 7, Cycle 10, Cycle 13, Cycle 16 (HbA1c)

Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18 (Testosterone)

Analytical Method(s) :

For each variable, summaries (1) to (2) will be provided.

For applicable variables, summaries (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots
Plots Over Time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables will be generated showing changes in NCI CTCAE grade from baseline to the worst postbaseline value.

7.11.3 Vital Signs

7.11.3.1 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse

Respiratory rate

SpO2

Body temperature

Weight

Visit: Baseline, Cycle 1 Day8, Day 15, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18

Analytical

Method(s) : For each variable, summaries (1) to (3) will be provided.

For applicable variables, summaries (4) will be provided.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Summary of Shifts of Vital Signs Parameters
Shift tables will be generated showing changes in NCI CTCAE grade from baseline to the worst postbaseline value.

7.11.4 12-Lead ECGs

Analysis Set: Safety Analysis Set

Analysis Variable(s) : 12-Lead ECG Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

QT Interval

QTcF Interval

Visit: Baseline, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, Cycle 7, Cycle 8, Cycle 9, Cycle 10, Cycle 11, Cycle 12, Cycle 13, Cycle 14, Cycle 15, Cycle 16, Cycle 17, Cycle 18

Analytical Method(s) : For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided.

For applicable variables, summary (3) will be provided.

For 12-lead ECG interpretation, summary (4) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters

Overall frequency distributions of MAV during treatment period will be provided. If an ECG laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Summary of Shift of 12-lead ECG Interpretation
Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.11.5 Other Observations Related to Safety

Not applicable

7.12 Interim Analysis

In this study, a 2-stage design will be used. An interim analysis for both futility and efficacy will be conducted in Stage 1, according to H1-minimax design in Englert. The proportion of patients achieving a confirmed objective response, per IRC, will be used as the endpoint for the interim analysis. The interim analysis will be performed with the first 29 patients in the main cohort of the expansion part at the cycle 6 after entry of the 29th patient. Enrollment will not be suspended during evaluation of these 29 patients; however, patients enrolled after the 29th patient in the main cohort of the expansion part will not be included in the interim analysis even if their ORR results were available on the cutoff date.

If the number of patients with confirmed ORR is 3 or fewer of the 29 patients, enrollment will be stopped entirely for futility. Additionally, if the number of patients with confirmed ORR is 10 or more of the 29 patients, it will be decided that brigatinib has demonstrated sufficient efficacy to reject the null hypothesis and declare superiority to the uninteresting ORR of 15% but the result at the timing of primary analysis will be interpreted descriptively. Otherwise, the study will continue until the 47 patients have had the opportunity to complete the Cycle 6 disease assessment. For the primary analysis, if the number of patients with confirmed ORR at the primary analysis is more than the number determined by the number at the interim analysis mentioned in Table 7.b, it will be decided that brigatinib has demonstrated sufficient efficacy to reject the null hypothesis. Of note, for the first 29 patients, their efficacy evaluation at the interim analysis were to be used.

Table 7.b Minimum Number of Confirmed ORR at the Primary Analysis

No. ORR at Interim Analysis	No. ORR at Primary Analysis
4/29	13/47
5/29	13/47
6/29	13/47
7/29	13/47
8/29	13/47
9/29	12/47

An IDMC will be formed. The IDMC will provide recommendation on the go/no go decision to move from the safety evaluation lead-in part to the expansion part, and on the futility and efficacy assessments performed at the interim analysis.

Furthermore for the publishment, the analysis only in safety lead-in part will be performed when all patients in safety lead-in part have had the oppotunity to complet the cycle 6.

7.12.1 Analysis plan at the Interim Analysis

The analysis plan at interim analysis is based on this document except the following things.

1. The definition of FAS-P is a subset of the FAS population consisting of first 29 patients in the main cohort of the expansion part.
2. The point estimate mentioned in section 7.8.1.1 will be calculated based on the maximum likelihood estimation.
3. The interim analysis will be done for the all subjects who enroll the study until first 29 patients in the main cohort of the expansion part enroll the study.

7.12.2 Analysis plan in safety lead-in part

The analysis plan will be done as follows in 9 patients in safety lead-in part instead of analysis population specified in SAP.

1. Same analysis as section 7.4, 7.7, 7.8.1.2, 7.8.2.1, 7.9.1.2, 7.11.1.1, and 7.11.1.2 will be performed.
2. Same analysis as (1) and (3) in section 7.9.1.1 will be performed.
3. Same analysis as (1), (4), (5), (6), (9), (10), (11), (12), (13), (14), (15), (16), and (17) in section 7.11.1.3 will be performed.
4. The analysis for best response in target lesions in section 7.8.2.3 will be performed.

7.13 Planned Analysis for the Refractory Patients and one for TKI-naïve Patients

7.13.1 Planned Analysis for the Refractory Patients

The analysis for the refractory patients will be performed when all refractory patients have had the opportunity to complete the Cycle 7 Day 1 disease assessment. The data for TKI-naïve Patients will be excluded from the analysis.

7.13.2 Planned Analysis for TKI-naïve Patients

The analysis for TKI-naïve Patients will be performed after the final database lock at the end of the study. For efficacy and pharmacokinetic analysis, the same analysis described in section 7.8 to 7.9 as the one for the refractory patients will be performed only in TKI-naïve Patient. Additionally, 12 months PFS rate as assessed by an IRC, per RECIST version 1.1 in the TKI-naïve expansion cohort will be performed as primary endpoint. For disposition of subjects, demographic, compliance, and safety analysis, the same analysis described in section 7.3 to 7.7, and 7.11 as the one for the refractory patients will be performed in TKI-naïve Patient and in all patients who have been enrolled.

7.13.3 Planned Final Analysis

For efficacy analysis, the analysis described in section 7.8 to 7.9 will be performed in following population.

- TKI-naïve Patients.
- Refractory Patients.

For disposition of subjects, demographic, compliance, and safety analysis, the same analysis described in section 7.3 to 7.7, and 7.11 will be performed in following population

- TKI-naïve Patients.
- Refractory Patients.
- All patients who have been enrolled.

7.14 Changes in the Statistical Analysis Plan

Based on comment from the team members, the following things has been changed.

- The analysis for photosensitivity event as special interest AE has been added.
- The analysis which was done in adhoc analysis has been added as additional analysis.
- Section 7.13.3 has been added.

8.0 REFERENCES

Englert S, Kieser M. Improving the flexibility and efficiency of phase II designs for oncology trials. Biometrics 2012;68(3):886-92.

Kunzmann, K. and Kieser, M. Point estimation and p values in phase II adaptive two-stage designs with binary endpoint. Statistics in Medicine 2017; 36, 971–984.

EORTC QLQ-C30 Scoring Manual (3rd edition). Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. Brussels: EORTC, 2001. ISBN: 2-9300 64-22-6.

Ikeda S, Shiroiwa T, Igarashi A, Noto S, Fukuda T, and Saito S, Shimozuma K. Developing a Japanese version of the EQ-5D-5L value set. Journal of the National Institute of Public Health, 2015 64(1), 47-55.

Appendix 1 Criteria for Markedly Abnormal Values

For each parameter except upper MAV Criteria of QTcF Interval, all evaluable data (ie, non-missing data) will be classified as a MAV or not. The criteria in the table below will be used.

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

12-lead ECG

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	-

For upper MAV Criteria of QTcF Interval, all evaluable data (ie, non-missing data) will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

For each subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that meets any of the following will be considered as a subject without MAV.

- Observed value is less than 450 msec and not missing.
- Change from baseline is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
QTcF Interval (msec)	-	If either of the following conditions is met: • observed value >=500 • change from baseline >= 30 and observed value >=450

Appendix 2 Definition of Adverse Event of GI events, Hepatic events and Visual Impairment Events

- GI events

Search criteria	PT_CODE (a)	PT_NAME (a)
SMQ: Gastrointestinal nonspecific symptoms and therapeutic procedures	10000059	Abdominal discomfort
	10000060	Abdominal distension
	10000081	Abdominal pain
	10000084	Abdominal pain lower
	10000087	Abdominal pain upper
	10060926	Abdominal symptom
	10000097	Abdominal tenderness
	10063541	Bowel movement irregularity
	10008399	Change of bowel habit
	10010774	Constipation
	10012735	Diarrhoea
	10079120	Discoloured vomit
	10053155	Epigastric discomfort
	10015137	Eructation
	10016766	Flatulence
	10017367	Frequent bowel movements
	10017999	Gastrointestinal pain
	10067715	Gastrointestinal sounds abnormal
	10059024	Gastrointestinal toxicity
	10059158	Infrequent bowel movements
	10028813	Nausea
	10062501	Non-cardiac chest pain
	10053634	Oesophageal discomfort
	10030180	Oesophageal pain
	10047700	Vomiting
Other PTs	10013950	Dysphagia
	10070840	Gastrointestinal tract irritation
	10067171	Regurgitation
	10038776	Retching
	10047708	Vomiting projectile

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- Hepatic events

Search criteria	PT_CODE (a)	PT_NAME (a)
SMQ: Liver related investigations, signs and symptoms	10001547	Alanine aminotransferase abnormal
	10001551	Alanine aminotransferase increased
	10003477	Aspartate aminotransferase abnormal
	10003481	Aspartate aminotransferase increased
	10067718	Bilirubin conjugated abnormal
	10004685	Bilirubin conjugated increased
	10077356	Bilirubin urine present
	10004792	Biopsy liver abnormal
	10058477	Blood bilirubin abnormal
	10005364	Blood bilirubin increased
	10005370	Blood bilirubin unconjugated increased
	10078360	Computerised tomogram liver abnormal
	10052554	Foetor hepaticus
	10059710	Galactose elimination capacity test abnormal
	10059712	Galactose elimination capacity test decreased
	10017688	Gamma-glutamyltransferase abnormal
	10017693	Gamma-glutamyltransferase increased
	10051333	Guanase increased
	10019621	Hepaplastin abnormal
	10019622	Hepaplastin decreased
	10068997	Hepatic artery flow decreased
	10062685	Hepatic enzyme abnormal
	10060794	Hepatic enzyme decreased
	10060795	Hepatic enzyme increased
	10019670	Hepatic function abnormal
	10067365	Hepatic hydrothorax
	10076254	Hepatic hypertrophy
	10057110	Hepatic mass
	10019705	Hepatic pain
	10066244	Hepatic sequestration
	10068358	Hepatic vascular resistance increased
	10066195	Hepatobiliary scan abnormal
	10019842	Hepatomegaly
	10019847	Hepatosplenomegaly
	10020575	Hyperammonaemia
	10020578	Hyperbilirubinaemia

Search criteria	PT_CODE (a)	PT_NAME (a)
	10051924	Hypercholia
	10068237	Hypertransaminasaemia
	10024690	Liver function test abnormal
	10077677	Liver function test decreased
	10077692	Liver function test increased
	10052550	Liver induration
	10075895	Liver palpable
	10061947	Liver scan abnormal
	10024712	Liver tenderness
	10064712	Mitochondrial aspartate aminotransferase increased
	10049631	Oedema due to hepatic disease
	10054125	Perihepatic discomfort
	10067338	Retrograde portal vein flow
	10064558	Total bile acids increased
	10062688	Transaminases abnormal
	10054889	Transaminases increased
	10045428	Ultrasound liver abnormal
	10050792	Urine bilirubin increased
	10056536	X-ray hepatobiliary abnormal
	10059571	Blood alkaline phosphatase abnormal
	10059570	Blood alkaline phosphatase increased
	10071634	Deficiency of bile secretion
	10049483	Glutamate dehydrogenase increased
	10080824	Glycocholic acid increased
	10059766	Haemorrhagic ascites
	10074084	Hepatic fibrosis marker abnormal
	10074413	Hepatic fibrosis marker increased
	10079686	Hepatic lymphocytic infiltration
	10020942	Hypoalbuminaemia
	10077291	Model for end stage liver disease score abnormal
	10077292	Model for end stage liver disease score increased
	10068821	Periportal oedema
	10069000	Peritoneal fluid protein abnormal
	10068999	Peritoneal fluid protein decreased
	10068998	Peritoneal fluid protein increased
	10082832	AST/ALT ratio abnormal

Search criteria	PT_CODE (a)	PT_NAME (a)
	10084058	Congestive hepatopathy
	10083172	Hepatic venous pressure gradient abnormal
	10083171	Hepatic venous pressure gradient increased
	10084071	Liver opacity
	10083123	Magnetic resonance imaging liver abnormal
SMQ: Cholestasis and jaundice of hepatic origin	10061009	Bilirubin excretion disorder
	10048611	Cholaemia
	10008635	Cholestasis
	10067969	Cholestatic liver injury
	10064190	Cholestatic pruritus
	10072268	Drug-induced liver injury
	10019754	Hepatitis cholestatic
	10020578	Hyperbilirubinaemia
	10021209	Icterus index increased
	10023126	Jaundice
	10023129	Jaundice cholestatic
	10023136	Jaundice hepatocellular
	10066758	Mixed liver injury
	10058717	Ocular icterus
	10074151	Parenteral nutrition associated liver disease
	10071634	Deficiency of bile secretion
	10048245	Yellow skin
SMQ: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	10080860	Acquired hepatocerebral degeneration
	10000804	Acute hepatic failure
	10077305	Acute on chronic liver failure
	10070815	Acute yellow liver atrophy
	10003445	Ascites
	10003547	Asterixis
	10068547	Bacterascites
	10004659	Biliary cirrhosis
	10004664	Biliary fibrosis
	10082480	Cardiohepatic syndrome
	10067969	Cholestatic liver injury
	10057573	Chronic hepatic failure
	10010075	Coma hepatic
	10063075	Cryptogenic cirrhosis
	10071265	Diabetic hepatopathy
	10072268	Drug-induced liver injury
	10051010	Duodenal varices

Search criteria	PT_CODE (a)	PT_NAME (a)
	10072319	Gallbladder varices
	10076237	Gastric variceal injection
	10076238	Gastric variceal ligation
	10051012	Gastric varices
	10057572	Gastric varices haemorrhage
	10061997	Hepatectomy
	10019637	Hepatic atrophy
	10065274	Hepatic calcification
	10019641	Hepatic cirrhosis
	10019660	Hepatic encephalopathy
	10066599	Hepatic encephalopathy prophylaxis
	10019663	Hepatic failure
	10019668	Hepatic fibrosis
	10067365	Hepatic hydrothorax
	10064668	Hepatic infiltration eosinophilic
	10061998	Hepatic lesion
	10019692	Hepatic necrosis
	10077215	Hepatic steato-fibrosis
	10019708	Hepatic steatosis
	10019772	Hepatitis fulminant
	10062000	Hepatobiliary disease
	10053244	Hepatocellular foamy cell syndrome
	10019837	Hepatocellular injury
	10052274	Hepatopulmonary syndrome
	10019845	Hepatorenal failure
	10019846	Hepatorenal syndrome
	10019851	Hepatotoxicity
	10071502	Intestinal varices
	10078058	Intestinal varices haemorrhage
	10076640	Liver dialysis
	10024670	Liver disorder
	10067125	Liver injury
	10062040	Liver operation
	10024714	Liver transplant
	10025129	Lupoid hepatic cirrhosis
	10076204	Minimal hepatic encephalopathy
	10066758	Mixed liver injury
	10051081	Nodular regenerative hyperplasia
	10082249	Nonalcoholic fatty liver disease

Search criteria	PT_CODE (a)	PT_NAME (a)
	10053219	Non-alcoholic steatohepatitis
	10077259	Non-cirrhotic portal hypertension
	10049631	Oedema due to hepatic disease
	10030210	Oesophageal varices haemorrhage
	10073215	Peripancreatic varices
	10074726	Portal fibrosis
	10036200	Portal hypertension
	10079446	Portal hypertensive colopathy
	10068923	Portal hypertensive enteropathy
	10050897	Portal hypertensive gastropathy
	10073979	Portal vein cavernous transformation
	10073209	Portal vein dilatation
	10067281	Portopulmonary hypertension
	10080429	Primary biliary cholangitis
	10080679	Regenerative siderotic hepatic nodule
	10052279	Renal and liver transplant
	10067338	Retrograde portal vein flow
	10039012	Reye's syndrome
	10070953	Reynold's syndrome
	10067823	Splenic varices
	10068662	Splenic varices haemorrhage
	10076331	Steatohepatitis
	10056956	Subacute hepatic failure
	10056091	Varices oesophageal
	10072284	Varicose veins of abdominal wall
	10078438	White nipple sign
	10083521	Immune-mediated hepatic disorder
SMQ: Hepatitis, non-infectious	10066263	Acute graft versus host disease in liver
	10071198	Allergic hepatitis
	10080576	Alloimmune hepatitis
	10003827	Autoimmune hepatitis
	10072160	Chronic graft versus host disease in liver
	10008909	Chronic hepatitis
	10064676	Graft versus host disease in liver
	10019717	Hepatitis
	10019727	Hepatitis acute
	10019754	Hepatitis cholestatic
	10019755	Hepatitis chronic active
	10019759	Hepatitis chronic persistent

Search criteria	PT_CODE (a)	PT_NAME (a)
	10019772	Hepatitis fulminant
	10019795	Hepatitis toxic
	10078962	Immune-mediated hepatitis
	10023025	Ischaemic hepatitis
	10067737	Lupus hepatitis
	10053219	Non-alcoholic steatohepatitis
	10051015	Radiation hepatitis
	10076331	Steatohepatitis

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- Visual Impairment Events

Search criteria	PT_CODE (a)	PT_NAME (a)
HLGT: vision disorder	10000389	Accommodation disorder
	10001902	Amaurosis
	10001903	Amaurosis fugax
	10001906	Amblyopia
	10001912	Amblyopia strabismic
	10001914	Amblyopia tobacco
	10002534	Aniseikonia
	10002537	Anisometropia
	10003569	Astigmatism
	10005169	Blindness
	10005177	Blindness cortical
	10005178	Blindness day
	10005184	Blindness transient
	10005186	Blindness unilateral
	10008585	Chloropsia
	10008795	Chromatopsia
	10010051	Colour blindness acquired
	10012646	Diabetic blindness
	10013036	Diplopia
	10013892	Dyschromatopsia
	10015290	Erythropsia
	10019099	Halo vision
	10020675	Hypermetropia
	10028651	Myopia
	10029404	Night blindness
	10034962	Photopsia

Search criteria	PT_CODE (a)	PT_NAME (a)
	10036628	Presbyopia
	10038264	Refraction disorder
	10038266	Refractive amblyopia
	10039677	Scintillating scotoma
	10042441	Sudden visual loss
	10044245	Toxic optic neuropathy
	10047511	Vision abnormal neonatal
	10047513	Vision blurred
	10047531	Visual acuity reduced
	10047532	Visual acuity reduced transiently
	10047571	Visual impairment
	10048216	Xanthopsia
	10049155	Visual brightness
	10051819	Cyanopsia
	10052087	Oscillopsia
	10052128	Glare
	10053549	Altered visual depth perception
	10059397	Antimetropia
	10061322	Optic nerve disorder
	10061323	Optic neuropathy
	10063341	Metamorphopsia
	10063354	Charles Bonnet syndrome
	10064133	Loss of visual contrast sensitivity
	10067557	Dysmetropsia
	10068906	Computer vision syndrome
	10070917	Eccentric fixation
	10072729	Delayed dark adaptation
	10073286	Pathologic myopia
	10074928	Low luminance best-corrected visual acuity decreased
	10075919	Pseudomyopia
	10076241	Psychogenic visual disorder
	10076302	Optic nerve compression
	10076660	Cortical visual impairment
	10078300	Acute myopia
	10078508	Homonymous diplopia
	10078509	Heteronymous diplopia
	10079450	Visual snow syndrome
	10079805	Delayed light adaptation

Search criteria	PT_CODE (a)	PT_NAME (a)
	10081186	Central vision loss
SMQ: retinal disorder	10054881	Acquired pigmented retinopathy
	10079367	Acute macular outer retinopathy
	10074444	Acute zonal occult outer retinopathy
	10064930	Age-related macular degeneration
	10001903	Amaurosis fugax
	10002444	Angiogram retina abnormal
	10063452	Arteriosclerotic retinopathy
	10071578	Autoimmune retinopathy
	10004390	Benign neoplasm of retina
	10072959	Birdshot chorioretinopathy
	10008762	Chorioretinal atrophy
	10061763	Chorioretinal disorder
	10008766	Chorioretinal scar
	10008769	Chorioretinitis
	10063118	Chorioretinopathy
	10010050	Colour blindness
	10010051	Colour blindness acquired
	10010056	Colour vision tests abnormal
	10010057	Colour vision tests abnormal blue-yellow
	10010058	Colour vision tests abnormal red-green
	10071321	Commotio retinae
	10058202	Cystoid macular oedema
	10079805	Delayed light adaptation
	10071004	Detachment of macular retinal pigment epithelium
	10052501	Detachment of retinal pigment epithelium
	10012688	Diabetic retinal oedema
	10012689	Diabetic retinopathy
	10078228	Diffuse uveal melanocytic proliferation
	10075567	Dry age-related macular degeneration
	10015831	Extraocular retinoblastoma
	10015901	Exudative retinopathy
	10051045	Eye naevus
	10017520	Fundoscopy abnormal
	10081899	Hypotony maculopathy
	10077392	Immune recovery uveitis
	10073499	Internal limiting membrane peeling
	10073929	IRVAN syndrome

Search criteria	PT_CODE (a)	PT_NAME (a)
	10059239	Leukaemic retinopathy
	10049935	Lipaemia retinalis
	10025407	Macular cyst
	10025409	Macular degeneration
	10075873	Macular detachment
	10071392	Macular fibrosis
	10051058	Macular hole
	10065534	Macular ischaemia
	10025415	Macular oedema
	10025416	Macular opacity
	10071041	Macular pigmentation
	10060815	Macular pseudohole
	10025419	Macular reflex abnormal
	10065319	Macular rupture
	10063185	Macular scar
	10081199	Macular telangiectasia
	10025425	Maculopathy
	10026432	Malignant neoplasm of retina
	10063341	Metamorphopsia
	10079959	Myopic chorioretinal degeneration
	10080534	Myopic traction maculopathy
	10064997	Necrotising retinitis
	10071129	Neovascular age-related macular degeneration
	10062940	Neuropathy, ataxia, retinitis pigmentosa syndrome
	10074696	Noninfective chorioretinitis
	10074699	Noninfective retinitis
	10081568	Non-proliferative retinopathy
	10065311	Paraneoplastic retinopathy
	10034962	Photopsia
	10037525	Pupillary light reflex tests abnormal
	10075189	Purtscher retinopathy
	10064714	Radiation retinopathy
	10064145	Retinal aneurysm
	10079121	Retinal aneurysm rupture
	10038824	Retinal arteriovenous malformation
	10038826	Retinal artery embolism
	10038827	Retinal artery occlusion

Search criteria	PT_CODE (a)	PT_NAME (a)
	10038829	Retinal artery spasm
	10038830	Retinal artery stenosis
	10038831	Retinal artery thrombosis
	10077911	Retinal collateral vessels
	10052643	Retinal coloboma
	10074908	Retinal cryoablation
	10038839	Retinal cyst
	10038840	Retinal cyst excision
	10038845	Retinal degeneration
	10038846	Retinal depigmentation
	10038847	Retinal deposits
	10038848	Retinal detachment
	10038853	Retinal disorder
	10062776	Retinal drusen
	10038857	Retinal dystrophy
	10038862	Retinal exudates
	10071391	Retinal fibrosis
	10038866	Retinal function test abnormal
	10038867	Retinal haemorrhage
	10067848	Retinal implant
	10051742	Retinal infarction
	10064833	Retinal infiltrates
	10057430	Retinal injury
	10038871	Retinal ischaemia
	10038873	Retinal laser coagulation
	10057428	Retinal melanocytoma
	10038878	Retinal melanoma
	10052784	Retinal migraine
	10057407	Retinal neoplasm
	10055666	Retinal neovascularisation
	10038886	Retinal oedema
	10062107	Retinal operation
	10038891	Retinal pallor
	10071246	Retinal perivascular sheathing
	10069652	Retinal phototoxicity
	10062971	Retinal pigment epithelial tear
	10038893	Retinal pigment epitheliopathy
	10038894	Retinal pigmentation
	10038895	Retinal scar

Search criteria	PT_CODE (a)	PT_NAME (a)
	10038897	Retinal tear
	10038899	Retinal telangiectasia
	10077890	Retinal thickening
	10048955	Retinal toxicity
	10067870	Retinal transplant
	10038900	Retinal tumour excision
	10038901	Retinal vascular disorder
	10038903	Retinal vascular occlusion
	10062108	Retinal vascular thrombosis
	10038905	Retinal vasculitis
	10038907	Retinal vein occlusion
	10038908	Retinal vein thrombosis
	10081463	Retinal vein varices
	10073562	Retinal vessel avulsion
	10079569	Retinal white without pressure
	10038910	Retinitis
	10038914	Retinitis pigmentosa
	10038916	Retinoblastoma
	10059663	Retinogram abnormal
	10038923	Retinopathy
	10051447	Retinopathy haemorrhagic
	10038926	Retinopathy hypertensive
	10038930	Retinopathy hyperviscosity
	10038933	Retinopathy of prematurity
	10038934	Retinopathy proliferative
	10038935	Retinopathy sickle cell
	10038936	Retinopathy solar
	10066985	Retinopexy
	10061492	Retinoschisis
	10065569	Rhegmatogenous retinal detachment
	10039677	Scintillating scotoma
	10066785	Scleral buckling surgery
	10040114	Serous retinal detachment
	10081652	Serpiginous choroiditis
	10062958	Subretinal fibrosis
	10069356	Subretinal fluid
	10071935	Subretinal haematoma
	10082240	Subretinal hyperreflective exudation
	10080316	Tractional retinal detachment

Search criteria	PT_CODE (a)	PT_NAME (a)
	10045178	Tunnel vision
	10065622	Venous stasis retinopathy
	10047567	Visual field tests abnormal
	10066421	Vitreal cells
	10047644	Vitrectomy
	10071035	Vitreomacular interface abnormal
	10057435	Vitreous adhesions
	10047650	Vitreous detachment
	10047651	Vitreous disorder
	10047654	Vitreous floaters
	10071936	Vitreous haematoma
	10047655	Vitreous haemorrhage
	10077514	Vitreous haze
	10047663	Vitritis
	10081123	Autoimmune eye disorder
	10005169	Blindness
	10005184	Blindness transient
	10005186	Blindness unilateral
	10081186	Central vision loss
	10008795	Chromatopsia
	10081428	Ciliary body melanoma
	10013892	Dyschromatopsia
	10015916	Eye disorder
	10079891	Eye haematoma
	10015926	Eye haemorrhage
	10078394	Eye opacity
	10081445	Foveal reflex abnormal
	10077000	Hypertensive cerebrovascular disease
	10071934	Intraocular haematoma
	10081061	Intra-ocular injection complication
	10076430	Intravitreal implant
	10053150	Leukocoria
	10074928	Low luminance best-corrected visual acuity decreased
	10069385	Ocular ischaemic syndrome
	10075324	Ocular lymphoma
	10082039	Ocular stem cell transplant
	10081144	Ophthalmic artery thrombosis
	10074349	Ophthalmic vein thrombosis

Search criteria	PT_CODE (a)	PT_NAME (a)
	10073561	Optical coherence tomography abnormal
	10034051	Pars plana cyst
	10073286	Pathologic myopia
	10034960	Photophobia
	10074603	Red reflex abnormal
	10081068	Sclerotomy
	10071573	Susac's syndrome
	10081431	Uveal melanoma
	10047513	Vision blurred
	10047531	Visual acuity reduced
	10047534	Visual acuity tests abnormal
	10047555	Visual field defect
	10047571	Visual impairment
	10082001	Vogt-Koyanagi-Harada disease
	10048216	Xanthopsia
	10071989	Vascular endothelial growth factor overexpression
	10082802	Disruption of the photoreceptor inner segment-outer segment
	10083006	Eye infarction
	10083087	Fluorescence angiogram abnormal
	10083329	Foveal degeneration
	10082768	Hyperaesthesia eye
	10083069	Immune-mediated uveitis
	10082596	Optic disc traction syndrome
	10083565	Orbital haematoma
	10083187	Serous retinopathy
	10083502	Tessellated fundus
	10083563	Transpupillary thermotherapy
	10031045	Orbital haemorrhage
	10048896	Retinal fovea disorder
	10071181	Vitreoretinal traction syndrome
SMQ: glaucoma	10001902	Amaurosis
	10001903	Amaurosis fugax
	10071364	Anterior chamber angle neovascularisation
	10069166	Blebitis
	10005169	Blindness
	10005178	Blindness day
	10005184	Blindness transient

Search criteria	PT_CODE (a)	PT_NAME (a)
	10005186	Blindness unilateral
	10007739	Cataract
	10061769	Ciliary body operation
	10069165	Conjunctival filtering bleb leak
	10080692	Coreoplasty
	10079171	Deep anterior chamber of the eye
	10072729	Delayed dark adaptation
	10014456	Electrooculogram abnormal
	10074027	Exfoliation syndrome
	10072289	Eye colour change
	10057105	Eye laser surgery
	10015958	Eye pain
	10016059	Facial pain
	10052128	Glare
	10077986	Goniotomy
	10022943	Iridoschisis
	10022948	Iris atrophy
	10057420	Iris operation
	10074928	Low luminance best-corrected visual acuity decreased
	10068960	Narrow anterior chamber angle
	10029404	Night blindness
	10030041	Ocular hyperaemia
	10081144	Ophthalmic artery thrombosis
	10074349	Ophthalmic vein thrombosis
	10048544	Ophthalmodynamometry abnormal
	10061321	Optic disc disorder
	10034546	Periorbital pain
	10034960	Photophobia
	10037520	Pupillary block
	10059663	Retinogram abnormal
	10081068	Sclerotomy
	10067126	Seidel test positive
	10066418	Tenon's cyst
	10047513	Vision blurred
	10047531	Visual acuity reduced
	10047532	Visual acuity reduced transiently
	10047549	Visual evoked potentials abnormal
	10047571	Visual impairment

Search criteria	PT_CODE (a)	PT_NAME (a)
	10082768	Hyperaesthesia eye
	10083516	Iris discolouration
SMQ: lens disorder	10054045	Anterior capsule contraction
	10063937	Capsular block syndrome
	10008795	Chromatopsia
	10012369	Deposit eye
	10078228	Diffuse uveal melanocytic proliferation
	10013892	Dyschromatopsia
	10078394	Eye opacity
	10024203	Lens dislocation
	10061219	Lens disorder
	10071370	Lens extraction
	10052980	Lenticular operation
	10074928	Low luminance best-corrected visual acuity decreased
	10082039	Ocular stem cell transplant
	10074603	Red reflex abnormal
	10047513	Vision blurred
	10047531	Visual acuity reduced
	10047571	Visual impairment
other PTs	10000173	Abnormal sensation in eye
	10071684	Anterior chamber collapse
	10002683	Anterior chamber opacity
	10070497	Aqueous humour leakage
	10003552	Asthenopia
	10081123	Autoimmune eye disorder
	10008422	Chemical burns of eye
	10010804	Contact lens intolerance
	10012369	Deposit eye
	10013774	Dry eye
	10015911	Eye burns
	10015916	Eye disorder
	10015943	Eye inflammation
	10061128	Eye injury
	10015946	Eye irritation
	10078394	Eye opacity
	10081699	Eye pH abnormal
	10081700	Eye pH decreased
	10081701	Eye pH increased

Search criteria	PT_CODE (a)	PT_NAME (a)
	10073423	Eye ulcer
	10016760	Flat anterior chamber of eye
	10051116	Foreign body sensation in eyes
	10074563	Graft versus host disease in eye
	10020939	Hypoaesthesia eye
	10072139	Ocular rosacea
	10082449	Ocular surface squamous neoplasia
	10061137	Ocular toxicity
	10056836	Ophthalmological examination abnormal
	10034960	Photophobia
	10042530	Superficial injury of eye
	10073692	Tear break up time decreased
	10049267	Thermal burns of eye
	10061412	Vitamin A deficiency eye disorder
	10048221	Xerophthalmia
	10001903	Amaurosis fugax
	10001906	Amblyopia
	10003230	Arteritis
	10075688	Autoimmune demyelinating disease
	10081123	Autoimmune eye disorder
	10005169	Blindness
	10005184	Blindness transient
	10005185	Blindness traumatic
	10005186	Blindness unilateral
	10081186	Central vision loss
	10008087	Cerebral arteritis
	10008795	Chromatopsia
	10010051	Colour blindness acquired
	10010056	Colour vision tests abnormal
	10061094	Cranial nerve injury
	10072729	Delayed dark adaptation
	10076456	Delayed myelination
	10012305	Demyelination
	10013892	Dyschromatopsia
	10049020	Encephalitis periaxialis diffusa
	10015923	Eye excision
	10061852	Eye operation
	10069060	Eye prosthesis insertion
	10069061	Eye prosthesis removal

Search criteria	PT_CODE (a)	PT_NAME (a)
	10017520	Fundoscopy abnormal
	10019452	Hemianopia
	10019455	Hemianopia heteronymous
	10019456	Hemianopia homonymous
	10077000	Hypertensive cerebrovascular disease
	10064133	Loss of visual contrast sensitivity
	10074928	Low luminance best-corrected visual acuity decreased
	10029404	Night blindness
	10069385	Ocular ischaemic syndrome
	10081144	Ophthalmic artery thrombosis
	10056836	Ophthalmological examination abnormal
	10030949	Optic pathway injury
	10065372	Orbitotomy
	10077820	Quadrantanopia
	10063613	Radiotherapy to eye
	10038956	Retro-orbital neoplasm
	10039677	Scintillating scotoma
	10045178	Tunnel vision
	10067485	Uhthoff's phenomenon
	10047531	Visual acuity reduced
	10047532	Visual acuity reduced transiently
	10047534	Visual acuity tests abnormal
	10047555	Visual field defect
	10047567	Visual field tests abnormal
	10047571	Visual impairment
	10061411	Visual pathway disorder
	10061412	Vitamin A deficiency eye disorder

(a) MedDRA version 23.0.

- Photosensitivity

Search criteria	PT_CODE (a)	PT_NAME (a)
All PTs of HLT: Photosensitivity and photodermatosis conditions	10000616	Actinic prurigo
	10019165	Hartnup disease
	10023269	Juvenile spring eruption
	10034972	Photosensitivity reaction
	10036087	Polymorphic light eruption
	10041303	Solar dermatitis
	10042496	Sunburn
	10051246	Photodermatosis
	10053396	Injection site photosensitivity reaction
	10058730	Application site photosensitivity reaction
	10065486	Infusion site photosensitivity reaction
	10068388	Actinic elastosis
	10072578	Chronic actinic dermatitis
	10073415	Implant site photosensitivity
	10075961	Administration site photosensitivity reaction
	10076137	Medical device site photosensitivity reaction
	10076186	Vaccination site photosensitivity reaction
	10083442	Hydroa vacciniforme

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD		